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Cardiovascular Injury and Repair in Chronic Obstructive Pulmonary Disease

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Cardiovascular disease represents a considerable burden in terms of both morbidity and mortality in patients with chronic obstructive pulmonary disease (COPD). For 20 years, forced expiratory volume in 1 second (FEV₁) has been an established predictor of cardiovascular mortality among smokers, never-smokers, and patients with COPD. We review evidence for increased cardiovascular risk in COPD. In addition, we assess the emerging evidence which suggests that hypoxia, systemic inflammation, and oxidative stress in patients with COPD may cause cardiovascular disease. We also discuss alternative hypotheses that the endothelium and connective tissues in the arteries and lungs of patients with COPD and cardiovascular disease have a shared susceptibility to these factors.

Keywords: COPD; cardiovascular disease; systemic inflammation; endothelial dysfunction

Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory disease of the lungs with a complex pathology involving large (chronic bronchitis) and small (bronchiolitis) airways, lung parenchyma (emphysema), and the pulmonary vasculature. In addition to pathology in the lungs, COPD is now believed to have systemic features (1, 2), and this has been recognized in the definition of COPD in recent guidelines (3, 4). An increase in the risk of cardiovascular disease is one such systemic feature (5). There is now considerable evidence of an association between COPD and cardiovascular disease, which will be reviewed in this article, together with the mechanisms which may underlie this association.

AIRFLOW LIMITATION AND CARDIOVASCULAR RISK

A number of population studies have shown that FEV₁ is a predictor of cardiovascular risk, even after adjusting for known cardiovascular risk factors such as age, sex, smoking, cholesterol, and education level/social class (Table 1) (6). In the Third National Health and Nutrition Examination Survey (NHANES III), 1,861 subjects who were 40 to 60 years of age at baseline assessment were followed and their cardiovascular mortality assessed. The group in the lowest quintile for FEV₁ had the highest risk of cardiovascular mortality (relative risk [RR], 3.36; 95% confidence interval [CI], 1.54–7.34) and had a fivefold increase in the risk of death from ischemic heart disease, compared with the quintile with the highest FEV₁. Similar relationships between FEV₁ and cardiovascular mortality have been shown in other large cohort studies, including the Framingham Heart Study and the Copenhagen City Heart study (6–11) (Table 1). Moreover, reduced FEV₁/FVC ratio, which is a more

specific indicator of airflow limitation than FEV₁, is also an independent risk factor for coronary events (RR, 1.30) (12). There appears to be no threshold in the relationship between cardiovascular risk and FEV₁; indeed, FEV₁% predicted is associated with cardiovascular risk even in never-smokers (8).

There is also a relationship between the rate of decline in FEV₁ and cardiovascular disease. In the Malmö “men born in 1914 study,” there were 56 cardiovascular events per 1,000 person-years in smokers in the highest tertile of decline in FEV₁, and 22.7 in the group with the lowest tertile (12, 13). The Baltimore Longitudinal Study of Ageing (14) showed that those individuals who had the most rapid decline in FEV₁ over a follow-up period of 16 years were three to five times more likely to die from a cardiac cause than those who had the slowest decline in FEV₁. This association was also found even among lifetime nonsmokers, suggesting that the relationship between change in FEV₁ and cardiovascular events is independent of the effects of smoking. In addition, NHANES III patients with severe airflow limitation (defined as an FEV₁ < 50% predicted and an FEV₁/FVC ratio ≤ 70%) were 2.1 times more likely to have electrocardiographic evidence suggestive of a prior myocardial infarction (5).

The FEV₁ is also an independent predictor of cardiovascular mortality in COPD. The Lung Health Study reported that for every 10% decrease in FEV₁, there was an increase of approximately 28% in fatal coronary events, and 20% in nonfatal coronary events, among subjects with mild to moderate COPD (15).

However, low FEV₁ is not *specifically* associated with risk from cardiovascular disease. Indeed, low baseline FEV₁ predicts stroke mortality (16), as well all-cause cancer mortality, and death from nonrespiratory, noncardiovascular causes (8). As such, FEV₁ may simply be a marker of exposure to a wide range of determinants of health that are difficult to adjust for statistically, such as poor nutrition and exposure to environmental pollution (including second-hand smoke). However, another possibility is that individuals with lower FEV₁ might have an enhanced inflammatory response to such stimuli, increased susceptibility to inflammation, or impaired healing. Only a proportion of individuals, even with significant cigarette smoke exposure, develop COPD (17), and similar hypotheses have been suggested to explain this observation (18).

CARDIOVASCULAR MORTALITY AND MORBIDITY IN COPD

Cardiovascular mortality is a leading, but underrecognized, cause of death in patients with COPD. In the Tucson Epidemiological Study of Airways Obstructive Disease (19), nearly 50% of those patients in whom obstructive airways disease was mentioned as a contributing cause of death had a cardiovascular cause as the primary cause. In a healthcare database study, which included 11,493 COPD patients followed up over 3 years, a three- to fourfold increased mortality rate from cardiovascular disease was found in patients with COPD (RR, 2.07; 95% CI, 1.82–2.36), compared with age- and sex-matched control subjects without COPD. Patients with COPD had a higher risk of congestive cardiac failure (RR, 4.09), arrhythmia (RR, 2.81), and acute myocardial infarction (RR, 1.51) (20).

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TABLE 1. SELECTED COHORT STUDIES PROVIDING EVIDENCE FOR AN ASSOCIATION BETWEEN FEV₁ AND CARDIOVASCULAR MORTALITY

Author	Sample Size	Follow-up (yr)	Mean Age (yr)	Lung Function	Relationship	Adjusted for
Hole (17) Renfrew, UK	15,411	15	44–64	FEV ₁ 1st to 5th quintile ranged from 73–113% predicted	Increase in RR of 1.56 in cardiovascular mortality comparing highest with lowest quintile	Age, smoking, serum cholesterol, BMI, social class
Ebi-Kryston (16) Whitehall Study, UK	17,717	10	40–64	FEV ₁ < 65%	Chronic phlegm production associated with all-causes and respiratory disease mortality, but not after adjusting for reduced FEV ₁	Age, smoking, employment grade, BP, antihypertensive medication, cholesterol, diabetes, ECG, IHD Hx.
Schunnehan (88) Buffalo Study, US	1,195	29	47	FEV ₁ 1st to 5th quintile ranged from 80–114% predicted	Increase in RR of 2.11 in cardiovascular mortality comparing highest with lowest quintile	Age, smoking, BP, BMI, education status
Persson (18) Sweden, Europe	1,462	12	38–60	PEFR 123–545 L · min ⁻¹	PEFR inversely proportional to risk of death from myocardial infarction	Age, height, BMI, waist/hip ratio, chest deformity, pulmonary disease, smoking, lipid levels, BP, diabetes, and physical activity
Truelsen (19) Copenhagen City Heart study, Europe	12,878	up to 17	45–84	FEV ₁	808 strokes RR 1.05 for each 10% decrease in FEV ₁ % predicted. Similar risk for stroke mortality	Sex, age, smoking, inhalation, BMI, systolic blood pressure, triglycerides, physical activity in leisure time, education, diabetes mellitus, and antihypertensive treatment
Hozawa (25) Atherosclerosis Risk In Communities Study, US	13,842	Up to 13	45–64	FEV ₁ percent predicted quartiles	Relative hazards 1.59, 1.52, 1.26, and 1.00 for each quartile of FEV ₁ % predicted, in White Americans, no association in African Americans	Age, sex, race, education, smoking status, BMI, WHR, vWF, ethanol intake, HDL cholesterol, systolic BP, antihypertensive medication, diabetes, WBC count and fibrinogen. Association not found in African Americans.

Definition of abbreviations: BMI = body mass index; BP = blood pressure; HDL = high-density lipoprotein; PEFR = peak expiratory flow rate; RR = relative risk; vWF = von Willebrand factor; WBC = white blood cell; WHR = waist/hip ratio.

In patients with established cardiovascular disease, COPD is associated with increased cardiovascular mortality. In a study of 4,284 patients who received treatment for coronary heart disease, mortality rates of 21% were noted over a 3-year follow up in patients diagnosed with COPD, compared with 9% in those without co-existing COPD (21). In an observational prospective study in patients after an acute myocardial infarction, 1-year mortality and re-hospitalization rates were significantly higher in patients with than in those without COPD (15.8% versus 5.7% and 48.7% versus 38.6%, respectively) (22). Furthermore, patients hospitalized for heart failure who also have COPD have a poorer prognosis, with an excess mortality, compared with heart failure patients without COPD (23).

Moreover, there is a higher risk of cardiovascular morbidity and hospitalization for cardiovascular disease in patients with COPD. In a retrospective matched cohort study from the Northern California Kaiser Permanent Medical Care Program involving 40,966 patients with COPD diagnosed between 1996 and 1999, the risk for hospitalization and cardiovascular disease was higher in patients with COPD (RR, 2.09; 95% CI, 1.99–2.20), than in age- and sex-matched control subjects (24). Younger patients (aged < 65 yr) and female patients had higher risk than older male participants. A further study from the Saskatchewan Health Service Database of 5,648 newly treated patients with COPD ≥ 55 years old, between 1990 and 1999, showed that cardiovascular morbidity and mortality were higher in patients with COPD than in the general population (RR, 1.9 and 2.0, respectively) (25).

In these studies morbidity and mortality data were obtained from routine data sources such as death certificates, which can

lead to diagnostic misclassification. However, in the Toward a Revolution in COPD Health (TORCH) trial, a large study of the effects of inhaled corticosteroids and long-acting β-agonists on mortality in COPD, where cause of death was accurately assessed by an adjudication panel, 25% of deaths were diagnosed as due to pulmonary causes and 27% to cardiovascular disease (26). Similarly, in the Lung Health Study an independent mortality and morbidity review board established cause of death and hospitalization in 5,887 patients with COPD aged 35 to 46 with mild to moderate airways obstruction over 5 years. This cohort had a 5-year mortality of 2.5%; of this, 25% died of a cardiovascular event, and cardiovascular disease accounted for 42% of the first hospitalization and 44% of the second hospitalization over a follow-up period in patients with relatively mild COPD, compared with 14% of hospitalization from respiratory causes (15).

Thus, a range of general population studies and studies in patients with COPD suggests that COPD may be an important risk factor for ischemic heart disease and sudden cardiac death. The mechanism responsible for the increased risk of cardiovascular disease in patients with COPD is not known; however, a number of hypotheses have been proposed (Figures 1 and 2).

SYSTEMIC INFLAMMATION AND CARDIOVASCULAR RISK IN COPD

The pathophysiology of atherosclerosis is complex (27). The role of lipid metabolism in atherosclerosis is long established. However, more recent studies have revealed the importance of

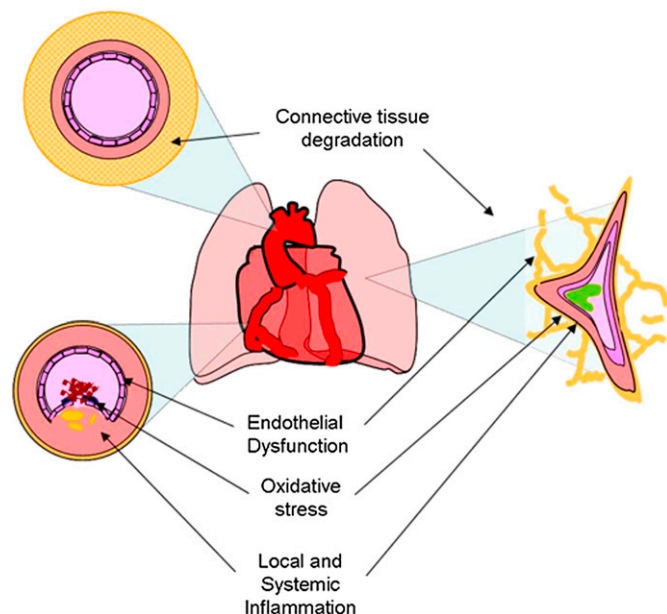


Figure 1. Pathophysiology in chronic obstructive pulmonary disease and coronary heart disease.

inflammation in plaque initiation, development, and rupture (28–30). The atherosclerotic process starts with injury to the vascular endothelium, which is made more permeable by a variety of factors, including systemic inflammation and oxidative stress. Lipoproteins then enter the intima via the vascular endothelium. Modified lipoproteins and systemic oxidative stress and inflammation induce cytokine production and increase the expression of cell adhesion molecules, such as ICAM-1 and VCAM-1, on the vascular endothelium, allowing circulating white blood cells to adhere to damaged endothelial surfaces. The release of chemotaxins directs migration of these leukocytes to the vascular intima. In this inflammatory environment, there is increased expression of scavenger receptors on monocytes/macrophages that ingest modified lipid lipoprotein particles, promoting the development of foam cells. Vascular smooth muscle cells then proliferate and may migrate from the media into the intima. These muscle cells produce extracellular matrix, which accumulates in the plaque with the formation of fibro-fatty lesions. This results in vessel wall fibrosis and consequent smooth muscle cell death. Calcification may occur, producing a plaque with a fibrous cap surrounding a lipid-rich core.

A number of cells and molecules can both promote and amplify this inflammatory process. Activated T-lymphocytes and macrophages can stimulate the release of cytokines, resulting

in endothelial activation. In addition to an increased expression of adhesion molecules on activated endothelium, cytokines such as interleukin (IL)-1, IL-6, and tumor necrosis factor α (TNF- α) can facilitate the deposition of components of atheromatous plaque formation. C-reactive protein (CRP) is an acute phase protein primarily produced by hepatocytes under the stimulation of IL-6 that is released after vascular damage. CRP, when released into the circulation, can up-regulate other inflammatory cytokines, activate complement, and promote the uptake of low density lipoproteins by macrophages. CRP also interacts with endothelial cells to stimulate the production of IL-6 and endothelin-1 (31, 32).

Stable atherosclerotic plaques are characterized by a thick fibrous cap and relatively little lipid accumulation. They progress relatively slowly and occlude the vessel lumen, resulting in angina pectoris. Vulnerable plaques, which contain large amounts of lipid and inflammatory cells, have a thin fibrous cap and are prone to rupture. After plaque rupture, lipids leak on to the arterial lumen and produce vasoconstriction and thrombus formation. The development of thrombus on a ruptured plaque is dependent on the fibrinolytic balance between the release of tissue type Plasminogen Activator (tPA) and Plasminogen Activator Inhibitor-1 (PAI-1).

The amount of thrombus formation determines the development of acute coronary syndromes in response to plaque rupture. In most cases, plaque rupture occurs asymptotically, since there is a fibrinolytic excess preventing the formation of thrombus (33). Systemic inflammation may also affect this process, as chronic smoking, passive smoking, and several inflammatory mediators appear to acutely inhibit endothelial tPA release. Thus, systemic inflammation is a potential mechanism in the development of atherosclerosis, and in addition, increased systemic inflammatory responses (associated with, for example, infection) are associated with acute cardiovascular events (34).

There is abundant evidence of increased systemic inflammation, both activated circulating leukocytes and increased inflammatory mediators in COPD (35). The origin of the systemic inflammatory response in COPD has not been clearly established, but a number of mechanisms have been proposed (reviewed in References 1 and 2). These include direct “spillover” of lung inflammation to the systemic circulation, an effect of lung hyperinflation, tissue hypoxia, muscle dysfunction, and bone marrow stimulation. Peripheral blood neutrophils are activated in patients with COPD to release reactive oxygen species (36), have increased expression of adhesion molecules (37), and demonstrate enhanced chemotaxis and extracellular proteolysis, mechanisms that are involved in the pathogenesis of atherosclerosis. For example, circulating monocytes from patients with COPD release 2.5-fold greater amounts of matrix metalloproteinase-9 (MMP9) than control subjects (38), and MMP9 has been implicated in the pathogenesis of arteriosclerosis and in plaque rupture (28).

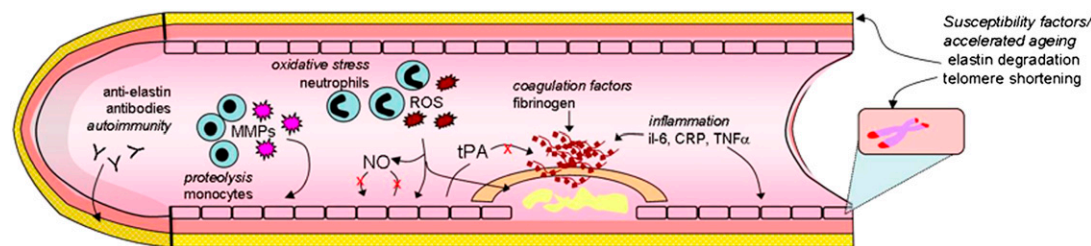


Figure 2. Putative mechanisms linking coronary heart disease and chronic obstructive pulmonary disease. hsCRP = high-sensitivity C-reactive protein; IL-6 = interleukin-6; MMPs = matrix metalloproteinases; NO = nitric oxide; ROS = reactive oxygen species; TNF- α = tumor necrosis factor α ; tPA = tissue plasminogen activator.

CRP is a biomarker of systemic inflammation. In addition, it is a marker of increased mortality in both COPD and in the general population (39), and is also a marker of increased cardiovascular risk (40). CRP is also found in atheromatous lesions and may therefore have a causal role in atherogenesis (41). Studies *in vitro* have shown that CRP adversely affects vasomotor endothelial function through the inhibition of endothelial nitric oxide synthase and consequently the production of nitric oxide (NO). Endothelial fibrinolysis is also impaired by CRP, which induces the production of PAI-1 (42, 43). A number of other inflammatory biomarkers have also been implicated in plaque formation, such as IL-7, IL-8, TNF- α , and fibrinogen (44–46).

A large number of studies have shown increases in circulating CRP levels in patients with COPD, which occurs with increased frequency as the disease progresses (47). In stable COPD there is an inverse relationship between CRP and airflow limitation, 6-minute walking distance, and body mass index (5, 39). An inverse relationship also exists between CRP concentrations and measures of pulmonary function in subjects without pulmonary disease and in never-smokers (48). There is an interaction between cigarette smoking and lung function on CRP levels. In the NHANES study the odds ratio of having an elevated CRP was increased in smokers and in subjects with a low FEV₁. However, the presence of smoking and a low FEV₁ increased the odds ratio of having an increased CRP even higher (49).

The Framingham Risk Score, the most widely used tool for predicting risk of cardiovascular events, is improved by adding CRP to the prediction models (50). In the NHANES study the severity of airflow limitation and the CRP were related to the cardiac infarction injury score (CIIS) (50). The CIIS is an electrocardiographic coding scheme to assess cardiac injury and is related to cardiovascular mortality (51). In this study the cohort was divided according to the degree of airflow limitation (none, mild, moderate, and severe) and the groups matched for lipid profile, although blood pressure and smoking history were higher in those with severe airflow obstruction. Patients with more severe airflow limitation had both a higher CRP level and a higher CIIS. The presence of severe airflow limitation and high CRP were associated with an even higher CIIS (5).

The level of the CRP also relates to outcomes in COPD. In a cohort of 1,302 individuals with airflow limitation, selected from the Copenhagen City Heart Study, individuals with baseline CRP greater than 3mg/L had a higher risk of hospitalization and death from COPD (hazard ratios 1.4, 25% CI, 1.0–2.0; and 2.2, 25% CI, 1.2–3.9, respectively), compared with individuals with a baseline CRP less than or equal to 3 mg/L adjusted for age, sex, FEV₁% predicted, tobacco consumption, and ischemic heart disease (52). Systemic inflammation is also associated with atheroma burden and increased cardiovascular risk, as well as with endothelial dysfunction after myocardial infarction. However, it remains unclear whether systemic inflammation is a cause of cardiovascular disease, or merely a marker.

SYSTEMIC OXIDATIVE STRESS IN COPD AND CARDIOVASCULAR DISEASE

No studies have directly assessed the hypothesis that increased systemic oxidative stress in COPD produces increased cardiovascular risk. Age, sex, obesity, cigarette smoking, hypertension, diabetes mellitus, and dyslipidemias are known risk factors for atherosclerosis which impair endothelial function, smooth muscle function, and vessel wall metabolism. These risk factors are associated with increased systemic oxidative stress (53). It is recognized that oxidative stress plays a pivotal role in the pathogenesis of atherosclerosis, particularly its detrimental effects on vascular endothelial function (54).

Reactive oxygen species (ROS), particularly oxygen radicals, injure cell membranes and nuclei and interact with endogenous vasoactive mediators formed in endothelial cells and so modulate vasomotion and the atherogenic process. ROS also cause lipid peroxidation, leading to the formation of oxidized lipoproteins (LDL), one of the key mediators of atherosclerosis. Oxidized LDLs are involved in the development of atherosclerosis by a number of mechanisms. They cause cholesterol ester accumulation in macrophages, and by their cytotoxic actions on monocytes cause inhibition of macrophage motility (55). Oxidized LDLs also cause up-regulation of adhesion molecules on the vascular endothelium leading to stimulation of monocytes, macrophages, platelets, and T-lymphocytes in the endothelial wall. ROS also mediate many of the responses to vascular injury, such as the impairment of vessel tone, promotion of inflammatory responses, leukocyte migration and adhesion, increased smooth muscle cell migration, proliferation, and apoptosis (56).

COPD has been associated with both local pulmonary and systemic oxidative stress. Peripheral blood neutrophils harvested from patients with COPD produce more ROS than those from normal subjects, and are associated with increased plasma levels of nitrotyrosine and products of lipid peroxidation as markers of oxidative stress (57). The increased oxidative stress that occurs during exacerbations of COPD, together with the enhanced systemic inflammatory response, have the potential to increase plaque instability, leading to plaque rupture, and may also alter fibrinolytic balance, making thrombosis more likely after plaque rupture and consequent acute coronary syndromes.

HYPOXIA AND CARDIOVASCULAR DISEASE

Patients with COPD are subject to hypoxia—either sustained hypoxia in patients with severe disease and respiratory failure, or intermittent hypoxia, for example during exercise or exacerbations. However, there is a threshold effect for hypoxia in patients with COPD related to the severity of the airflow limitation, which does not apply to the relationship between pulmonary function and cardiovascular risk. Hypoxia has been shown to have a number of effects that influence atherogenesis. These include increasing systemic inflammation and oxidative stress, up-regulating cell adhesion molecules, and inducing hemodynamic stress (58–60). Increased foam cell production, a critical constituent of unstable atherosclerotic plaques, is also stimulated when macrophages are exposed to hypoxic conditions (58). The cellular adhesion molecules ICAM-1 and P-selectin have been shown to be up-regulated by hypoxic challenge in human umbilical endothelial cells (59), and CRP also increases in response to hypoxic conditions (60). Hypoxia can also induce increased oxidative stress. In an animal model, hypoxia produced atherosclerosis in the presence of dyslipidemia and increased lipid peroxidation, a marker of oxidative stress (61), and reduced levels of the antioxidant superoxide dismutase are found in the myocardial tissue of rats exposed to hypoxic environments (62).

Hypoxia also induces hemodynamic stress (63). Normal subjects exposed to an hypoxic challenge to reduce oxygen saturations to 80% for 1 hour developed an increased heart rate and cardiac index. These effects of acute and intermittent hypoxia may have relevance for individuals with COPD, who are subjected to intermittent hypoxic episodes during exertion and exacerbations. Hypoxia also affects the renal circulation, reducing renal blood flow and activating the renin angiotensin system, resulting in increased peripheral vasoconstriction and oxidative stress (64).

EFFECTS ON THE SYMPATHETIC SYSTEM AND CARDIOVASCULAR RISK

Activation of the sympathetic nervous system (SNS) is associated with increased risk of cardiovascular disease (65), which, given that both COPD and chronic respiratory failure are associated with SNS activation (66), may contribute to the cardiovascular morbidity and mortality observed in patients with COPD.

Several studies have found that a high resting heart rate is an independent risk factor for CV morbidity and mortality in the general population, and resting tachycardia is common in COPD (67). Furthermore, COPD is also associated with reduced heart rate variability, a marker of abnormal cardiac autonomic regulation, which has been found to predict mortality in the elderly (68, 69).

In view of the potential adverse effects of sympathetic stimulation, and the beneficial effects of β -receptor antagonists in heart failure, atrial fibrillation, and myocardial infarction, several observational studies have examined the effects of β -agonists on cardiovascular morbidity and mortality, with conflicting results (70–72). However, the recent TORCH study found no increase in all-cause or cardiovascular mortality in 1,521 patients treated with salmeterol (a long-acting β -agonist), compared with the 1,524 patients allocated to placebo (73).

In a meta-analysis including 131 patients with COPD randomized to either a cardioselective β -blockers or placebo, FEV₁ was not significantly different in patients treated with β -blockers (74). Moreover, evidence from observational studies suggests that cardioselective β -blockers reduce mortality in patients with COPD after vascular surgery, myocardial infarction, or admission to hospital with acute exacerbation of COPD (75–77), although in such studies it is difficult to avoid residual confounding by disease severity. Nevertheless, there remains a reluctance to use β -blockers in patients with COPD (78), despite the joint recommendation of the American College of Cardiology and American Heart Association that β -blockers should not be routinely withheld in patients with COPD who have heart failure or a recent non ST-elevation myocardial infarction (79, 80).

VASCULAR DYSFUNCTION

Considerable interest has focused on the vasculature as a potential explanatory mechanism for the association between COPD and cardiovascular risk, with particular focus on endothelial dysfunction and changes in arterial stiffness.

Central arterial stiffness, as measured by aortic pulse wave velocity (PWV), has been shown to predict cardiovascular mortality in longitudinal studies in a range of populations, involving over 12,000 subjects in total, independent of age, sex, smoking history, cholesterol, and mean arterial blood pressure. PWV quantifies arterial stiffness by measuring the transit-time of the pressure wave from the heart to the femoral artery. In healthy compliant arteries there is a slow transit time for the wave, and in stiffer arteries the pressure wave moves more quickly. PWV more closely reflects the pathologic state of central arteries and is better associated with coronary atheroma burden and with known risk factors such as smoking than peripheral blood pressure (81–83).

Arterial stiffness has been associated with airflow limitation. Zureik and coworkers (84) found that PWV was associated with FEV₁ in 194 ostensibly healthy middle-aged men, independent of age, sex, and smoking status, although Taneda and colleagues (85) were unable to replicate this finding in 678 healthy Japanese Americans. Therefore, reduced pulmonary function may be associated with arterial stiffness in healthy individuals.

Sabit and coworkers (86) found that arterial stiffness was increased in patients with COPD, compared with controls matched

for a number of cardiovascular risk factors, and that arterial stiffness was higher in patients with more severe COPD than in those with mild to moderate disease. Augmentation pressure (a measure of central arterial pressure obtained via analysis of the arterial wave form at the radial artery), was also found to be increased in patients with COPD compared with healthy control subjects matched for age, sex, and smoking history, independent of co-existing cardiovascular morbidity (87). PWV is associated with markers of systemic inflammation in healthy individuals (88) and in patients with COPD. Sabit and colleagues (86) found a correlation between IL-6 and aortic PWV, and Mills and coworkers (87) showed a relationship between CRP concentrations and augmentation pressure. Therefore, systemic inflammation may contribute to the increased arterial stiffness found in patients with COPD.

One mechanism, by which systemic inflammation could modify arterial function, is via the endothelium. Pulmonary vascular endothelial dysfunction is well established in patients with COPD (89), and there is recent evidence that endothelial dysfunction may be abnormal in the systemic circulation. Barr and coworkers (90) found that flow-mediated dilatation, a method for assessing endothelial function, was related to airflow obstruction in ex-smokers with and without COPD. Another potential mechanism to explain the association proposed in this article was that endothelial dysfunction might cause COPD as well as causing cardiovascular disease in COPD, as the association between FMD and FEV₁ was *not* independent of CT measured emphysema severity.

A further mechanism linking COPD to systemic arterial abnormalities is the failure of repair both in the lungs and in the vascular endothelium. Endothelial progenitor cells (EPCs) are pluripotent stem cells derived from the bone marrow that participate in vascular repair and angiogenesis, and a reduction in EPCs has been implicated in atherothrombogenesis (91). Low circulating endothelial progenitor cells predict future cardiovascular events (92). Circulating EPCs are decreased in the systemic vasculature of patients with COPD (93), although paradoxically they appear to be increased in the pulmonary vasculature (94). Reduced EPCs may result in a failure to repair vascular abnormalities.

CONNECTIVE TISSUE DEGRADATION

Emphysema severity, quantified by CT scanning, is also related to brachial artery stiffness, independent of age, sex, and pack-years smoked. In arteries, elastin degradation is associated with increased collagen; larger, thicker arteries; and increased stiffness (95). Similarly, elastin degradation in the lung leads to loss of alveolar attachments, decreased compliance, increased collagen, and emphysema (96). Skin wrinkling, which is characterized by elastin degradation in the dermis (elastosis) (97), has also been found to be associated with CT emphysema severity, independent of pack-years smoked (98).

Increased elastolytic activity has also been implicated in the development of both arterial stiffness and emphysema severity. A polymorphism in gelatinase B (MMP-9) is associated with increased risk of arterial stiffness and is associated with upper zone dominant emphysema (99). Increased levels of MMP-9 are found both in bronchoalveolar lavage (100) and sputum (101) in subjects with emphysema, and levels of MMP-9 are increased in the serum of subjects with arterial stiffness (102). MMP-12 (macrophage elastase) knockout mice are protected against cigarette smoke-induced emphysema compared with wild-type mice (103), and MMP-12/apoE-deficient mice are protected against elastin degradation in atherosclerosis compared with single-deficiency apoE mice (104). Thus, enhanced proteolytic

activity and subsequent elastin degradation could be the mechanism linking emphysema and arterial wall stiffness.

It has also been proposed that autoimmunity in COPD might be responsible for the systemic features of the condition (105). Lee and colleagues (106) reported that patients with COPD and emphysema, compared with control subjects without COPD and emphysema, had increased B cell and T cell responses to elastin peptides, as well as increased circulating antielastin antibodies.

ACCELERATED AGING, ATHEROSCLEROSIS, AND COPD

Aging is an important determinant of both arterial stiffening and the development of emphysema, and is also a key cause of skin wrinkling and osteoporosis (107, 108). Consequently, there has been some interest in aging as a mechanism of disease in patients with COPD (109).

Although cigarette smoke exposure is the main cause of COPD, individuals vary in their susceptibility to its effects. COPD preferentially affects elderly individuals, with those older than 65 years having a higher risk, independent of their history of exposure to tobacco smoke. The reasons for this remain unclear.

Many of the features of COPD are also seen with normal aging among never-smokers. Progressive decline in lung function, a characteristic feature of COPD, also occurs with age in healthy individuals (17). Aging lungs also show progressive distal airspace enlargement, associated with elastin fibrin fragmentation and loss of elasticity, resulting in an emphysema-like condition (107, 110).

Animal models of ageing produced by defects in "aging genes," such as senescence protein-30 (111) or klotho gene (112, 113), have a shortened lifespan and develop a syndrome resembling accelerated aging with skin wrinkling, osteoporosis, emphysema, and arterial stiffness (109). A similar phenotype is found among patients with COPD. Therefore, COPD may be a condition of accelerated aging.

Aging is characterized by shortening of the DNA component of telomeres, the specialized segments located at the end of eukaryotic chromosomes which protect them from degradation and recombination (114). In most somatic cells telomeres shorten with every cell cycle, and systemic oxidative stress and inflammation enhance this shortening process (115).

Telomere length (TL) therefore reflects replication history of cells, but is also a reflection of cumulative oxidative stress and chronic inflammation acting on progenitor cells (116), and provides a marker of biological age. Peripheral blood leukocytes (PBL) are often used to measure TL in humans, and TL in blood leukocytes also accords with that in other tissues (117). Shorter telomeres in blood leukocytes correlate with a poor survival, due principally to a higher mortality from heart and infectious diseases (117–119). Interestingly, there is a dose-dependent relationship between leukocyte telomere shortening and pack-years smoked (120). Furthermore, alveolar epithelial and endothelial cells from patients with emphysema exhibit greater telomere shortening, compared with those from subjects without emphysema. There is also evidence of increased markers of cell senescence and apoptosis in alveolar cells as a consequence of telomere shortening in emphysematous lungs (121). Cellular senescence is associated with shortened or damaged telomeres and is characterized by permanent exit from the cell cycle, morphologic changes, and altered function. Senescent cells show increased release of cytokines and chemokines and enhanced matrix metalloprotease activity (122), which are potential mechanisms for the enhanced inflammation and tissue destruction in emphysema. Accelerated aging, as measured by telomere short-

ening, has also been linked to cardiovascular disease (123). Telomere length is a predictor of cardiovascular events (118), and reduced leukocyte telomere length is associated with all-cause mortality in patients with stable coronary disease (123). A relationship has also been shown between telomere length and PWV (124). Interestingly, statin therapy appears to increase telomere length and improve survival (118).

Shorter telomeres have been detected in senescent endothelial cells and vascular smooth muscle cells from human atherosclerotic plaques (125–128). Furthermore, shorter telomeres have been found in endothelial cells in patients with coronary artery disease compared with those from age-matched patients without coronary disease, and in atherosclerotic coronary endothelial cells compared with those from nonatherosclerotic sites (126). Senescent cells promote endothelial dysfunction and hence atherosclerosis, and appear to be implicated in plaque destabilization (127, 128).

Animal models of telomerase deficiency result in progressive telomere shortening and consequent cell senescence, and develop premature aging-associated disorders including atherosclerosis, cardiac dysfunction, and sudden death (129, 130). These studies suggest that endothelial dysfunction and senescence induced by telomere shortening may play a critical role in coronary atherogenesis.

Therefore, accelerated aging, characterized by shortening of the DNA component of telomeres, might cause vascular and pulmonary disease via mechanisms we have already discussed, such as increased systemic inflammation, connective tissue destruction, and endothelial dysfunction.

Accelerated aging processes may therefore be the link for the association between COPD and increased cardiovascular risk.

EFFECTS OF TREATMENT ON CARDIOVASCULAR END POINTS

Emerging evidence of the important consequences of the systemic effects of COPD, particularly adverse cardiovascular effects, has led to consideration of potential therapies directed at these systemic effects. Since it has been considered, but not yet proven, that systemic inflammation is a mechanism for the increased risk of cardiovascular disease in COPD, this has provided the rationale to consider using novel therapeutic interventions that target this response, either directly or indirectly by reducing lung inflammation (131). There is circumstantial evidence, but as yet no clinical trial which has demonstrated that treating systemic or lung inflammation in COPD reduces cardiovascular morbidity or mortality.

There is no evidence that the potential antiinflammatory effects of bronchodilators, either β -agonists or anticholinergics or theophyllines, have any effect on the systemic inflammation and consequent risk of cardiovascular disease.

Inhaled corticosteroids have the potential to reduce systemic inflammation. An initial report in a small number of subjects suggested that 2 weeks of treatment with inhaled (fluticasone 500 μ g twice daily) or oral corticosteroids (prednisolone 30 mg/d) could suppress systemic CRP levels by 50 and 63%, respectively, compared with placebo (132), and that this reduction might be linked with decreased cardiovascular events. However, a much larger randomized placebo-controlled trial failed to demonstrate any significant effect of 4 weeks of treatment with inhaled corticosteroids alone or in combination with long-acting β -agonists on CRP or IL-6 levels (133).

The effect of inhaled corticosteroids on the risk of acute myocardial infarction has been studied in a cohort of patients with COPD from the Saskatchewan health services database. In

this retrospective study, the use of inhaled corticosteroids (ICS) overall was not associated with a significant decrease in the risk of acute myocardial infarction (134). However, a 32% reduction in the risk of myocardial infarction was observed for low doses of ICS (50–200 µg/d) (134).

Statins have been shown to decrease mortality from cardiovascular disease and to lower CRP levels, probably because they also reduce the production of IL-6 (135). Experimentally, simvastatin inhibited cigarette smoking-induced emphysema and reduced the inflammatory-cell infiltrate in the lungs (136).

Retrospective pharmaco-epidemiologic studies have also indicated that statins reduce hospitalizations from exacerbations, acute coronary events, and cardiovascular and respiratory mortality among patients with COPD (137), and the combined use of statins and ICSs is associated with a more favorable prognosis than the use of a statin alone (138). A randomized controlled trial of the effects of statins in COPD is now needed.

Conflict of Interest Statement: W.M. has been reimbursed for attending conferences by GlaxoSmithKline (GSK), Zambon, and Boehringer Ingelheim and has received honoraria from GSK and Zambon for participating as a speaker at various scientific meetings. He serves on an Advisory Board for GSK and as a consultant for Pfizer, SMB Pharmaceuticals, and Galen. Research grants to support work carried out in his laboratory is provided by Pfizer for a Clinical Research Fellow, part funding for a Respiratory Research Nurse and a multi-center clinical trial; GSK for part funding of a Respiratory Research Nurse and a multi-center clinical trial, and Hoffmann La Roche for a multi-center clinical trial. J.M. has received reimbursement for travel expenses from GSK and Boehringer Ingelheim. D.M. has received reimbursement for travel expenses from GSK and Boehringer Ingelheim.

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